cations must surely be discarded. Equally, an overview which clearly states that it has used data from studies in which comparison of bleeding was not possible and then makes recommendations for clinical practice must be viewed with great caution.

In conclusion, we believe the following points should be made.

Firstly, it is time to define the minimum criteria before including studies in a meta-analysis.

Secondly, at present there is insufficient evidence to justify use of antiplatelet agents for thromboprophylaxis.

Thirdly, this meta-analysis has resulted in regressive recommendations which may lead to consideration of treatment with lesser efficacy and safety than currently available regimens with low dose heparins.

Fourthly, in view of these serious reservations we suggest that the recommendations of the antiplatelet trialists are not put into practice.

Finally, we agree that there is a need for well designed, large, blinded trials to compare antiplatelet and anticoagulant thromboprophylaxis.

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(Accepted 9 August 1994)

Antiplatelet therapy for thromboprophylaxis: the need for careful consideration of the evidence from randomised trials

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BMJ 1994;309:1215-7

Venous thrombosis and pulmonary embolism remain an important cause of morbidity and mortality both in surgical patients and in immobilised medical patients.[1-5] Various thromboprophylactic treatments have, therefore, been devised to prevent or limit thromboembolism. Our previous systematic overview (or meta-analysis) of randomised trials of perioperative subcutaneous heparin found that among surgical patients such treatment can roughly halve the risk not only of deep venous thrombosis but, more importantly, of pulmonary embolism[6] (see fig 1). Subcutaneous heparin is now widely recommended for surgical or medical patients at high risk of venous occlusion.[3-5]

Prospectively defined methods for overviews (meta-analyses)

The recent Antiplatelet Trialists' Collaboration overview of the thromboprophylactic effects of antiplatelet therapy used prospectively determined criteria for trial inclusion and treatment comparisons that were similar to those of the previous heparin overview.[6-8] The aim was to include all unconfounded properly randomised trials of antiplatelet versus no antiplatelet therapy (or of one antiplatelet regimen versus another) that could have been available for review by March 1990 in which deep venous thrombosis was systematically and unbiasedly monitored. (Parts I and III of the previous overview report give a fuller description of the methods used.[1,7] The appropriateness of using "assumption free" statistical methods rather than the "random effects" model when combining trial results, as when combining results from different centres in a multicentre trial, has been discussed in detail previously.[9,10]) Such randomised trials were to be included whether or not the treatment comparison was "blinded" by placebo control. This was also the case in the heparin overview, where exclusion of informative "open" trials (in particular, the important open international multicentre trial coordinated by Professor V V Kakkar[11]) would have been equally inappropriate. Analyses confined to placebo controlled studies, which may be less subject to treatment dependent biases in the assessment of subjective outcome measures, were, however, also considered separately (but, as was shown,[1] these would not materially alter the conclusions: see below).

When the data collected did not include information about the prospectively defined outcomes of interest among all patients initially randomly assigned, extra details were sought from the principal investigators.[1,7] It was often possible to obtain such information, but when it was not the available data were to be included in the overview—unless the numbers missing were so extensive that the comparison could no longer be considered properly randomised. For example, in the study by Soreff *et al* results of venographic follow up were available for only 14 of 25 patients allocated placebo and for 21 of 26 allocated aspirin.[12] So, although the pulmonary emboli data were to be included from this study, the venographically identi-

fied thromboses were not to be; their inclusion would not, however, alter the overall findings.

Similar reductions in thromboembolism observed with antiplatelet therapy and with subcutaneous heparin

Previously, it had generally been concluded that the randomised trials of antiplatelet prophylaxis had shown this treatment to have little or no effect on venous thrombosis or pulmonary embolism.[3-5] But the Antiplatelet Trialists' Collaboration overview of the findings among about 9000 randomised patients brings together far more evidence than was previously conveniently available. It shows that, like subcutaneous heparin, antiplatelet therapy (usually studied for only about one to three weeks) substantially reduces both the incidence of deep venous thrombosis and, particularly, the incidence of pulmonary embolism in a wide range of surgical patients (see fig 1). The limited evidence available in medical patients who are at high risk of thromboembolism is also encouraging.

Overall, among all patients allocated antiplatelet therapy in these trials the odds of deep venous thrombosis were significantly reduced by 39% (SD 5%)—which, as was explained,[1] corresponds to a risk reduction of about a quarter—and the odds of pulmonary embolism were significantly reduced by 64% (SD 10%) (fig 1). In principle, some of these results might have been somewhat biased by knowledge in open trials of which patients had been allocated antiplatelet therapy and which had been allocated control. In practice, however, this seems to have made little difference, which contradicts the previous article by Cohen and colleagues.[14] For, when the analyses were confined to those trials in which the controls were given a placebo, the odds reductions became 38% (SD 7%) for deep venous thrombosis and 65% (SD 11%) for pulmonary embolism—which are just as large as before and still highly significant (both two sided P values $<0{\cdot}00001$).

So, after making some allowance for the imperfect compliance with allocated treatment that inevitably

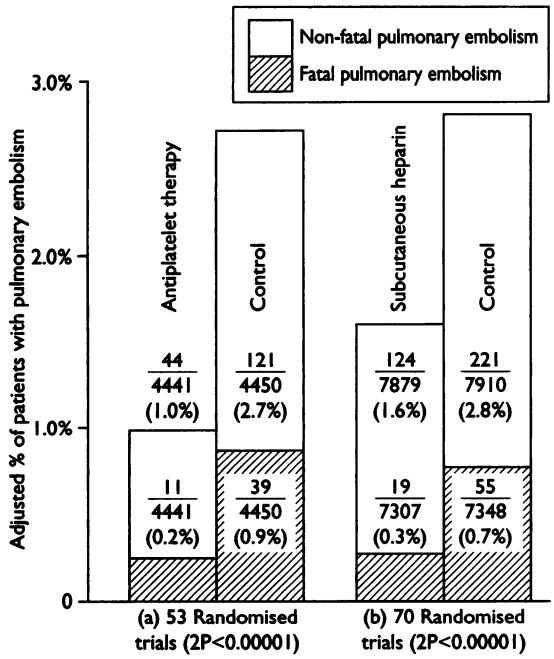

FIG 1—*Reductions in perioperative pulmonary embolism in randomised trial overviews of antiplatelet therapy and of subcutaneous heparin. (Results of a trial by Hume et al in elective orthopaedic surgery were inadvertently excluded, and their inclusion—0 pulmonary emboli among 37 patients allocated aspirin v 1 pulmonary embolus among 34 placebo controls[13]—would only slightly strengthen the overview findings for antiplatelet therapy)*

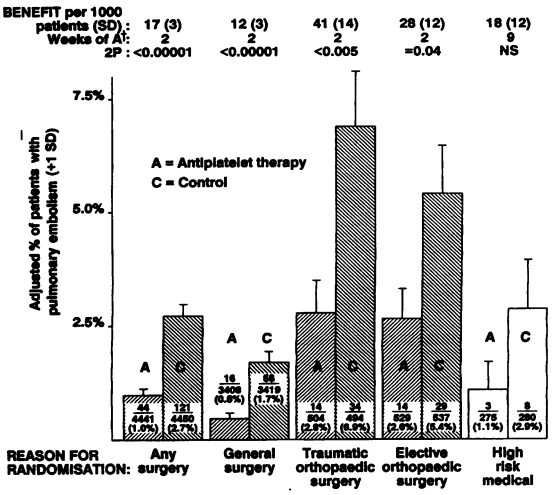

FIG 2—*Absolute effects of antiplatelet therapy on pulmonary embolism in trials that sought venous thrombosis systematically. Weeks of A= Means of scheduled antiplatelet durations. (Further information for the study of Chrisman et al was not available as the study records had been accidentally destroyed.[19] For the purpose of this subanalysis, therefore, the results among all of the patients—0 v 4 pulmonary emboli—were included in the elective orthopaedic surgery category, even though some patients had had fractures*

happens in clinical trials, the Antiplatelet Trialists' Collaboration report concluded that "it seems that a few weeks of antiplatelet therapy can almost halve the odds of suffering a deep venous thrombosis and can reduce pulmonary embolism by more than half."[1] It has been shown that long term antiplatelet therapy (such as one aspirin daily) is practicable and that, among patients at high risk of occlusive vascular disease, it reduces the risk of vascular death, myocardial infarction, stroke, and other vascular occlusion.[1,15] The risk of thromboembolism and of other serious occlusive vascular events can remain high for some months after surgery,[16-18] and so it seems reasonable to consider prolonged antiplatelet thromboprophylaxis—which, in contrast with most other available forms, would be practicable—for as long as the risk is still substantial.

Similar proportional reductions in pulmonary embolism imply greater benefit for those at higher risk

As discussed previously,[1,6,7] it is not the proportional but the absolute reductions that determine how worthwhile therapy is. The proportional reductions in deep venous thrombosis with antiplatelet therapy seemed to be similar in each main category of surgery—general surgery (37% (SD 8%) proportional reduction; $2P<0{\cdot}00001$), traumatic orthopaedic surgery (31% (SD 13%); $2P=0{\cdot}02$), elective orthopaedic surgery (49% (SD 11%); $2P<0{\cdot}0001$)—and in high risk medical patients. There was no significant heterogeneity of these odds reductions, as was also the case for subcutaneous heparin.[6] Similarly, the proportional reductions in pulmonary embolism seemed to be roughly the same in the different types of surgical patient—71% (SD 14%); $2P<0{\cdot}00001$, 60% (SD 20%); $2P<0{\cdot}005$, and 51% (SD 24%); $2P=0{\cdot}04$, respectively—and in high risk medical patients. If this is indeed the case, then the absolute benefits would be expected to be greatest for those at highest risk—for example, those undergoing orthopaedic surgery (fig 2).

Effects of antiplatelet therapy on surgical bleeding

In contrast with the suggestion of Cohen and colleagues,[14] the Antiplatelet Trialists' Collaboration report included—after substantial correspondence with the separate trialists—a particularly complete

Reported bleeding complications in trials of antiplatelet thromboprophylaxis among surgical patients that sought deep venous thrombosis systematically (Reproduced from reference 1)

Complication reported	No of trials with data	Antiplatelet group	Adjusted controls	Absolute excess per 1000 (SD)	Significance (one sided P value)
Fatal bleed	53	2/4441 (0·05%)	0/4450 (0%)	—	NS
Non-fatal "major" bleed*	45	28/3798 (0·7%)	15/3808 (0·4%)	3 (2)	=0·04
Reoperation, haematoma, or infection due to bleed	25	177/2269 (7·8%)	129/2306 (5·6%)	22 (9)	=0·003

*Major bleeds were prospectively defined as those that needed transfusion.

summary of the available data on the risks of significant bleeding associated with perioperative use of antiplatelet therapy (table). These risks seemed to be relatively small, with no significant difference between the treatment groups in fatal bleeds, and only a marginally significant excess of about three "major" bleeds (prospectively defined as the need for transfusion) per 1000 patients treated with antiplatelet therapy. (In comparison, there were 17 fewer pulmonary emboli per 1000 treated, six of which would have been fatal.) Information on other complications which might be related to bleeding—for example, reoperation, wound haematomas, and infections due to bleeding—was also quite commonly available, after correspondence, and there was a definite excess of about 22 per 1000 patients. Similar increases were seen when the analyses were confined to the, potentially less biased, placebo controlled studies.

Implications both for clinical practice and for research

Most trials assessed the thromboprophylactic efficacy of antiplatelet therapy in the absence of subcutaneous heparin, so that information on adding antiplatelet therapy to heparin was limited. For preventing pulmonary embolism, however, it did seem that the effects of antiplatelet therapy might be, at least in part, additive to those of heparin four (0·6%) of 654 patients allocated antiplatelet therapy plus heparin had pulmonary emboli recorded versus 11 (1·7%) of 653 patients allocated the same heparin regimen, which corresponds to an absolute difference of 11 pulmonary emboli per 1000 ($2P < 0·05$). These data are, however, sparse—as are data on the risks of bleeding with the combination of antiplatelet and anticoagulant therapy. Consequently, as was pointed out,[1] there is a need for some large randomised trials which could determine more reliably the types of patient in whom the major benefits outweigh the major risks and which could assess the relative merits of antiplatelet, anticoagulant, and combination therapy—using medium doses of aspirin (75-325 mg/day), which seem to be about as effective, while causing fewer side effects, as higher doses.[1] One such trial (the pulmonary embolism prevention trial[20]) aims to randomly allocate some 10 000 orthopaedic surgery patients in Europe, Australia, and New Zealand to one month of 162 mg aspirin daily or placebo, in addition to any other thromboprophylaxis (including subcutaneous heparin) considered to be indicated. Data from non-randomised comparisons [21 22] will not, however, suffice to address these questions due to the large potential biases inherent in such methods.[8]

As was emphasised previously,[1] treatment recommendations depend on a variety of considerations, of which trial results are only one part. Trial results—or, better, statistically definite overviews of them—provide information, not instructions, to those concerned with treatment. But when individual trials or overviews do—as for the effects of antiplatelet therapy on pulmonary embolism, on other serious vascular events, and on safety—produce definite results then surgeons and physicians with high risk patients should at least make themselves familiar with those results. This does not imply that some other effective thromboprophylaxis should not be used, but for patients at high risk other methods alone may not suffice. So, until the results from large trials become available, it would seem reasonable to conclude[1] that the present results "indicate that antiplatelet therapy—either alone or, *for greater effect* [our italics], in addition to other proved forms of thromboprophylaxis (such as subcutaneous heparin)—should be *considered* [our italics]" for patients who are at substantial risk of venous thromboembolism, many of whom do not currently receive any form of effective thromboprophylaxis.[23 24]

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